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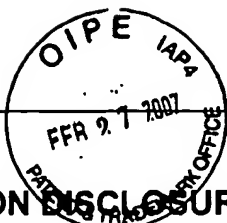
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| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br>( Not for submission under 37 CFR 1.99) | Application Number     |                     | 10696676   |  |
|   | Filing Date            |                     | 2003-10-29 |  |
|   | First Named Inventor   | Keith L. Black      |            |  |
|   | Art Unit               | 1635                |            |  |
|   | Examiner Name          | Richard A. SCHNIZER |            |  |
|   | Attorney Docket Number | 67789-503           |            |  |

| U.S.PATENTS  |         |                    |                        |                  |   |  |
|--|---------|--------------------|------------------------|------------------|---|--|
| Examiner Initial*  | Cite No | Patent Number      | Kind Code <sup>1</sup> | Issue Date       | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear |
| PS   | 1       | 5011837            |                        | 1991-04-30       | Atwal et al.                                    |  |
| I  | 2       | 5234922            |                        | 1993-08-10       | Welsh et al.                                    |  |
| I  | 3       | 7018979            |                        | 2006-03-28       | Black et al.                                    |  |
| PS   | 4       | 6417207            |                        | 2002-07-09       | Garvey et al.                                   |  |
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| PS   | 1       | 20030072748        |                        | 2003-04-17       | Black et al.                                    |  |
| PS   | 2       | 20020143188        |                        | 2003-10-03       | Garvey et al.                                   |  |
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| Examiner Initial* | Cite No | Foreign Document Number <sup>3</sup> | Country Code <sup>2i</sup> | Kind Code <sup>4</sup> | Publication Date | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear | T <sup>5</sup>           |
|-------------------|---------|--------------------------------------|----------------------------|------------------------|------------------|---|--|--------------------------|
| RS                | 1       | WO 01/54680                          |                            |                        | 2001-02-07       | Cedars-Sinai Medical Center                     |  | <input type="checkbox"/> |
| RS                | 2       | WO 96/12030                          |                            |                        | 1996-04-25       | Rhone-Poulenc Rorer S.A.                        |  | <input type="checkbox"/> |
| RS                | 3       | WO 01/54771                          |                            |                        | 2001-08-02       | Cedars-Sinai Medical Center                     |  | <input type="checkbox"/> |

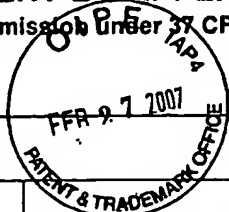
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**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T <sup>5</sup>           |
|--------------------|---------|---|--------------------------|
| RS                 | 1       | Black, Keith L. et al., Intracarotid infusion of RMP-7, a bradykinin analog, and transport of gallium-68 ethylenediamine tetraacetic acid into human gliomas, Journal of Neurosurgery, 86(4):603-609 (1997).  | <input type="checkbox"/> |
| I                  | 2       | Brayden, Joseph E., Functional roles of KATP channels in vascular smooth muscle, Clinical and Experimental Pharmacology and Physiology, 29(4):312-6 (2001).   | <input type="checkbox"/> |
| I                  | 3       | Brayden, J.E., Potassium channels in vascular smooth muscle, Clinical and Experimental Pharmacology and Physiology, 23(12): 1069-76 (December 1996). (ABSTRACT ONLY)  | <input type="checkbox"/> |
| I                  | 4       | Esaki, Takanori et al., Blockade of KATP channels with glibenclamide does not alter functional activation of cerebral blood flow in the unanesthetized rat, Brain Research, 948:56-63 (2002).   | <input type="checkbox"/> |
| RS                 | 5       | Hashizume, Kazuhiro et al., Increased endothelial vesicular transport correlates with increased blood-tumor barrier permeability induced by bradykinin and leukotriene C4, Journal of Neuropathology and Experimental Neurology, 61 (8):725-735 (August 2002).  | <input type="checkbox"/> |

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|    |   |                          |
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| 6  | Inamura, Takanori et al., Bradykinin selectively opens blood-tumor barrier in experimental brain tumors, Journal of Cerebral Blood Flow Metabolism, 14(5):862-870 (1994).   | <input type="checkbox"/> |
| 7  | Janigro, Damir et al., ATP-sensitive K <sup>+</sup> channels in rat aorta and brain microvascular endothelial cells, Department of Neurological Surgery, University of Washington, C812-C821 (1993).  | <input type="checkbox"/> |
| 8  | Joo, Ferenc et al., Regulation of the macromolecular transport in the brain microvessels: the role of cyclic GMP, Brain Research, 278:165-174 (1983).   | <input type="checkbox"/> |
| 9  | Liebner, Stefan et al., Claudin-1 and claudin-5 expression and tight junction morphology are altered in blood vessels of human glioblastoma multiforme, Acta Neuropathol, 100:323-331 (2000).   | <input type="checkbox"/> |
| 10 | Liu, Sju Ming et al., Nitric oxide and cGMP regulate endothelial permeability and F-actin distribution in hydrogen peroxide-treated endothelial cells, Experimental Cell Research, 235:238-244 (1997).  | <input type="checkbox"/> |
| 11 | Shah, Shrenik P. et al., Drug delivery to the central nervous system: a review, Journal of Pharmacy and Pharmaceutical Science, 6(2):252-273 (2003).  | <input type="checkbox"/> |
| 12 | Morimoto, Takashi et al., Increased levels of tissue endostatin in human malignant gliomas, Clinical Cancer Research, 8:2933-2938 (September 2002).   | <input type="checkbox"/> |
| 13 | Nilaver, Gajanan et al., Delivery of herpesvirus and adenovirus to nude rat intracerebral tumors after osmotic blood-brain barrier disruption, Proceedings of the National Academy of Science, 92:9829-9833 (October 1995).                                 | <input type="checkbox"/> |
| 14 | Ningaraj, Nagendra S. et al., Adenosine 5'-triphosphate-sensitive potassium channel-mediated blood-brain tumor barrier permeability increase in a rat brain tumor model, Cancer Research, 63:8899-8911 (December 15, 2003).                                 | <input type="checkbox"/> |
| 15 | Ningaraj, Nagendra S. et al., Calcium-dependent potassium channels as a target protein for modulation of the blood-brain tumor barrier, Drug News Perspect, 16(5):291-298 (June 2003).  | <input type="checkbox"/> |
| 16 | Rothberg, Brad S. et al., Gating kinetics of single large-conductance Ca <sup>2+</sup> -activated K <sup>+</sup> channels in high Ca <sup>2+</sup> suggest a two-tiered allosteric gating mechanism, Journal of General Physiology, 114:93-124 (July 1999). | <input type="checkbox"/> |

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|    |    |  |                          |
|----|----|--|--------------------------|
| PS | 17 | Schoch, Heike J. et al., Hypoxia-induced vascular endothelial growth factor expression causes vascular leakage in the brain, Brain, 125:2549-2557 (2002).  | <input type="checkbox"/> |
|    | 18 | Stewart, Patricia A., Endothelial vesicles in the blood-brain barrier: are they related to permeability?, Cellular and Molecular Neurobiology, 20(2):149-163 (2002).   | <input type="checkbox"/> |
|    | 19 | Sugita, Masao et al., Cyclic GMP-specific phosphodiesterase inhibition and intracarotid bradykinin infusion enhances permeability into brain tumors, Cancer Research, 58(5):914-920 (1998).  | <input type="checkbox"/> |
|    | 20 | Tanaka, Yoshio et al., Molecular constituents of maxi Kca channels in human coronary smooth muscle: predominant $\alpha$ + $\beta$ subunit complexes, Journal of Physiology, 502(3):545-557 (1997).  | <input type="checkbox"/> |
|    | 21 | Yokoshiki, Hisashi et al., ATP-sensitive K <sup>+</sup> channels in pancreatic, cardiac, and vascular smooth muscle cells, Invited Review, Department of Molecular and Cellular Physiology, College of Medicine, University of Cincinnati, Cincinnati, Ohio, C25-C37 (1998). | <input type="checkbox"/> |
|    | 22 | Mackic, Jasmina B. et al., Cereport (RMP-7) increases the permeability of human brain microvascular endothelial cell monolayers, Pharmaceutical Research, 16(9):1360-1365 (1999).  | <input type="checkbox"/> |
|    | 23 | Asotra, Kamlesh et al., Blood-brain barrier as portal for drug delivery, Advances in Clinical Neuroscience, 10:323-339 (2000).   | <input type="checkbox"/> |
|    | 24 | Uchida, Mikito et al., Cyclic GMP-dependent blood-brain tumor barrier permeability is not mediated by cyclic GMP-dependent protein kinase, Congress of Neurological Surgeons, San Antonio, TX (2000). (ABSTRACT ONLY)  | <input type="checkbox"/> |
|    | 25 | Ransom, Christopher et al., BK channels in human glioma cells, Journal of Neurophysiology, 85:790-803 (2001).  | <input type="checkbox"/> |
|    | 26 | Abdul, M. and Hoosein, N., Expression and activity of potassium ion channels in human prostate cancer, Cancer Letters, 186(1):99-105 (December 1, 2002). (ABSTRACT ONLY)   | <input type="checkbox"/> |
| PS | 27 | Abdul, M. and Hoosein, N.M., Voltage-gated potassium ion channels in colon cancer, Oncology Report, 9(5):961-964 (September-October 2002). (ABSTRACT ONLY)   | <input type="checkbox"/> |

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|           |    |  |                          |
|-----------|----|--|--------------------------|
| TS        | 28 | Abdul, M. et al., Activity of potassium channel-blockers in breast cancer, Anticancer Research, 23(4):3347-3351 (July-August 2003). (ABSTRACT ONLY)  | <input type="checkbox"/> |
|           | 29 | Baba, T. et al., Intracarotid infusion of leukotriene C4 selectively increases blood-brain barrier permeability after focal ischemia in rats, Journal of Cerebral Blood Flow and Metabolism, 11:638-643 (July 1991). (ABSTRACT ONLY) | <input type="checkbox"/> |
|           | 30 | Black, Keith L., Biochemical opening of the blood-brain barrier, Advance Drug Delivery Reviews, 15:37-52 (1995).   | <input type="checkbox"/> |
| IN<br>ST. | 31 | Black, Keith L., Imaging and drug delivery to tumor-infiltrated brain, Clinical Neurosurgery, Chapter 30: 563-572  | <input type="checkbox"/> |
| (1992)    | 32 | Black, Keith L. et al., Increased opening of blood-tumor barrier by leukotriene C4 is dependent on size of molecules, Neurological Research, 14: 402-404, (1992).  | <input type="checkbox"/> |
| ...       | 33 | Black, Keith L., Leukotriene C4 receptors in isolated brain capillaries, Advances in Prostaglandin Thromboxane and Leukotriene Research, 17:508-511(1987).   | <input type="checkbox"/> |
|           | 34 | Black, Keith L., Leukotrienes increase blood-brain barrier permeability following intraparenchymal injections in rats, Annals of Neurology, 18:3 349-351 (1985).   | <input type="checkbox"/> |
|           | 35 | Black, Keith L., Selective opening of blood-brain barrier for drug delivery to brain tumors, Perspectives in Neurological Surgery, 4:1 97-104 (1993).  | <input type="checkbox"/> |
|           | 36 | Chio, C.C. et al., Selective blood-tumor barrier disruption by leukotrienes, Journal of Neurosurgery, 77(3):407-410 (September 1992). (ABSTRACT ONLY)  | <input type="checkbox"/> |
|           | 37 | Cloughesy, T.F. et al., Intra-arterial carboplatin chemotherapy for brain tumors: a dose escalation study based on cerebral blood flow, Journal of Neuro-Oncology, 35(2):121-131 (November 1997). (ABSTRACT ONLY)                    | <input type="checkbox"/> |
| TS        | 38 | Cloughesy, T.F. et al., Intra-arterial cereport (RMP-7) and carboplatin: a dose escalation study of recurrent malignant gliomas, Neurosurgery, 44(2):270-279 (February 1999). (ABSTRACT ONLY)  | <input type="checkbox"/> |

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|    |    |   |                          |
|----|----|---|--------------------------|
| RS | 39 | Elliot, P.J. et al., Unlocking the blood-brain barrier: a role for RMP-7 in brain tumor therapy, Experimental Neurology, 141(2):214-224 (October 1996). (ABSTRACT ONLY)   | <input type="checkbox"/> |
|    | 40 | Lui, Y. et al., Correlation between bradykinin-induced blood-tumor barrier permeability and B2 receptor expression in experimental brain tumors, Neurological Research, 23(4):379-387 (June 2001). (ABSTRACT ONLY)                            | <input type="checkbox"/> |
|    | 41 | King, Wesley A. et al., Intracarotid infusion of leukotriene C4 increases blood-tumor barrier permeability in experimental rat brain tumors, Neurological Surgery Surgical Forum, Volume XL:490-493 (1989).                                   | <input type="checkbox"/> |
|    | 42 | Matsukado, K. et al., Steroids decrease uptake of carboplatin in rat gliomas - uptake improved by intracarotid infusion of bradykinin analog, RMP-7, Acta Neurochirurgica Supplement, 70:159-161 (1997). (ABSTRACT ONLY)                      | <input type="checkbox"/> |
|    | 43 | Matsukado, K. et al., Intracarotid low dose bradykinin infusion selectively increases tumor permeability through activation of bradykinin B2 receptors in malignant gliomas, Brain Research, 792(1):10-15 (May 4, 1998). (ABSTRACT ONLY)      | <input type="checkbox"/> |
|    | 44 | Nakano, S. et al., Enhanced cytokines delivery and intercellular adhesion molecule 1 (ICAM-1) expression in glioma by intracarotid infusion of bradykinin analog, RMP-7, Neurological Research, 19(5):501-508 (October 1997). (ABSTRACT ONLY) | <input type="checkbox"/> |
|    | 45 | Nomura, T. et al., Intracarotid infusion of bradykinin selectively increases blood-tumor permeability in 9L and C6 brain tumors, Brain Research, 659(1-2):62-66 (October 3, 1994). (ABSTRACT ONLY)  | <input type="checkbox"/> |
|    | 46 | Riley, M.G. et al., Intraarterial administration of carboplatin and the blood brain barrier permeabilizing agent, RMP-7: a toxicological evaluation in swine, Journal of Neuro-Oncology, 36(2):167-178 (January 1998). (ABSTRACT ONLY)        | <input type="checkbox"/> |
|    | 47 | Sugita, M. et al., Nitric oxide and cyclic GMP attenuate sensitivity of the blood-tumor barrier permeability to bradykinin, Neurological Research, 20(6):559-563 (September 1998). (ABSTRACT ONLY)  | <input type="checkbox"/> |
| RS | 48 | Woodford, K.A. et al., Inhibition of ATP-sensitive potassium channels causes reversible cell-cycle arrest in human breast cancer cells in tissue culture, Journal of Cell Physiology, 162(2):163-171 (February 1995). (ABSTRACT ONLY)         | <input type="checkbox"/> |

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|--------------------|---------|---|--------------------------|
| PJ                 | 49      | Bang et al., Nitroglycerin-mediated vasorelaxation is modulated by endothelial calcium-activated potassium channels, Cardiovascular Research, 43(3):772-778 (August 15, 1999). (ABSTRACT ONLY)  | <input type="checkbox"/> |
| I                  | 50      | Black, Keith L. et al., Selective opening of the blood-tumor barrier by intracarotid infusion of leukotriene C4, Journal of Neurosurgery, 72(99):912-916 (1990).  | <input type="checkbox"/> |
| I                  | 51      | Butt, E. et al., Inhibition of cyclic GMP-dependent protein kinase-mediated effects by (Rp)-8-bromo-PET-cyclic GMPS, British Journal of Pharmacology, 116(8): 3110-3116 (December 1995). (ABSTRACT ONLY)  | <input type="checkbox"/> |
| I                  | 52      | Chen, C.H. et al., Nitric oxide activates Ca2+-activated K+ channels in cultured bovine adrenal chromaffin cells, Neuroscience Letters, 248(2):127-129 (May 29, 1998). (ABSTRACT ONLY)  | <input type="checkbox"/> |
| I                  | 53      | Ferrero, R. et al., Comparative effects of several nitric oxide donors on intracellular cyclic GMP levels in bovine chromaffin cells: correlation with nitric oxide production, British Journal of Pharmacology, 127(3):779-787 (June 1999). (ABSTRACT ONLY)    | <input type="checkbox"/> |
| I                  | 54      | Fullerton, D.A. et al., Effective control of pulmonary vascular resistance with inhaled nitric oxide after cardiac operation, Journal of Thoracic Cardiovascular Surgery, 111(4):753-762; discussion 762-763 (April 1996). (ABSTRACT ONLY)                      | <input type="checkbox"/> |
| I                  | 55      | Gbadegesin, M. et al., Hypoxia modulated nitric oxide-induced regulation of NMDA receptor currents and neuronal cell death, American Journal of Physiology, 277(4 Pt 1):C673-683 (October 1999). (ABSTRACT ONLY)  | <input type="checkbox"/> |
| I                  | 56      | Goto, K. et al., Sympathetic control of arterial membrane potential by ATP-sensitive K(+)-channels, Hypertension, 35 (1 Pt 2):379-384 (January 2000) (ABSTRACT ONLY)  | <input type="checkbox"/> |
| I                  | 57      | Hardy, P. et al., A major role for prostacyclin in nitric oxide-induced ocular vasorelaxation in the piglet, Circulation Research, 83(7): 721-729 (October 5, 1998) (ABSTRACT ONLY)   | <input type="checkbox"/> |
| PJ                 | 58      | Jackson, W.F. et al., Prostacyclin-induced vasodilation in rabbit heart is mediated by ATP-sensitive potassium channels, American Journal of Physiology, 264(1 Pt 2):H238-43 (January 1993) (ABSTRACT ONLY)   | <input type="checkbox"/> |

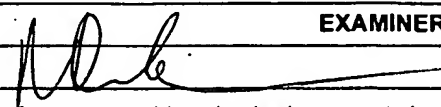
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|   |    |  |                          |
|---|----|--|--------------------------|
| B | 59 | Kieler-Jensen, N. et al., Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance, Journal of Heart and Lung Transplant, 13(3): 366-375 (May-June 1994) (ABSTRACT ONLY)  | <input type="checkbox"/> |
| 1 | 60 | Kurtz, A. et al., Mode of nitric oxide action on the renal vasculature, Acta Physiologica Scand, 168(1): 41-45 (January 2000) (ABSTRACT ONLY)  | <input type="checkbox"/> |
|   | 61 | Liu, Q. et al., Hypoxic dilation of porcine small coronary arteries: role of endothelium and KATP-channels, British Journal of Pharmacology, 120(4):728-734 (February 1997) (ABSTRACT ONLY)  | <input type="checkbox"/> |
|   | 62 | Patel, A.I. et al., Activation of guanosine 3', 5'-cyclic monophosphate (cGMP)-dependent protein kinase in rat vas deferens and distal colon is not accompanied by inhibition of contraction, Journal of Pharmacology and Experimental Therapeutics, 283(2): 894-900 (November 1994) (ABSTRACT ONLY) | <input type="checkbox"/> |
|   | 63 | Patel, A.I. and Diamond, J., Activation of guanosine 3', 5'-cyclic monophosphate (cGMP)-dependent protein kinase in rabbit aorta by nitroglycerin and sodium nitroprusside, Journal of Pharmacology and Experimental Therapeutics, 283(2):885-893 (November 1997) (ABSTRACT ONLY)                    | <input type="checkbox"/> |
|   | 64 | Rajek, A. et al., Inhaled nitric oxide reduces pulmonary vascular resistance more than prostaglandin E(1) during heart transplantation, Anesthesia and Analgesia, 90(3): 523-530 (March 2000) (ABSTRACT ONLY)  | <input type="checkbox"/> |
|   | 65 | Solina, A. et al., A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients, Journal of Cardiothoracic Vascular Anesthesia, 14(1):12-17 (February 2000) (ABSTRACT ONLY)  | <input type="checkbox"/> |
| B | 66 | Vaali, K. et al., Relaxing effects of NO donors on guinea pig trachea in vitro are mediated by calcium-sensitive potassium channels, Journal of Pharmacology and Experimental Therapeutics, 286(1): 110-114 (July 1998) (ABSTRACT ONLY)  | <input type="checkbox"/> |

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IN AN APPLICATION

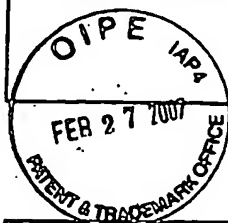
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Docket Number:  
CEDAR 043453Application Number:  
09/491,500

Applicant: Keith L. Black and Nagendra S. Ningara)

Filing Date: Jan. 26, 2000

Group Art Unit: 1646


**U.S. PATENT DOCUMENTS**

| EXAMINER<br>INITIAL | DOCUMENT NO. | DATE      | NAME               | CLASS | SUBCLASS | FILING DATE<br>IF APPROPRIATE |
|---------------------|--------------|-----------|--------------------|-------|----------|-------------------------------|
| DS                  | 5,112,596    | 05/12/92  | Malfroy-Camine     |       |          |                               |
|                     | 5,124,146    | 06/23/92  | Neuwelt            |       |          |                               |
|                     | 5,215,985    | 06/01/93  | Murphy et al.      |       |          |                               |
|                     | 5,234,947    | 08/10/93  | Cherksey           |       |          |                               |
|                     | 5,256,688    | 10/26/93  | Grover et al.      |       |          |                               |
|                     | 5,262,419    | 11/16/93  | Aberg et al.       |       |          |                               |
|                     | 5,268,164    | 12/07/93  | Kozarich et al.    |       |          |                               |
|                     | 5,314,887    | 05/24/94  | Aldrich et al.     |       |          |                               |
|                     | 5,399,587    | 03/21/95  | Garcia et al.      |       |          |                               |
|                     | 5,416,097    | 05/16/95  | Erhardt et al.     |       |          |                               |
|                     | 5,434,137    | 07/18/95  | Black              |       |          |                               |
|                     | 5,527,527    | 06/18/96* | Friden             |       |          |                               |
|                     | 5,527,778    | 06/18/96* | Black              |       |          |                               |
|                     | 5,578,599    | 11/26/96  | Diani et al.       |       |          |                               |
|                     | 5,604,198    | 02/18/97  | Poduslo et al.     |       |          |                               |
|                     | 5,670,477    | 09/23/97  | Poduslo et al.     |       |          |                               |
|                     | 5,677,344    | 10/14/97  | Greenfield et al.  |       |          |                               |
|                     | 5,679,706    | 10/21/97  | D'Alonzo et al.    |       |          |                               |
|                     | 5,686,416    | 11/11/97* | Kozarich et al.    |       |          |                               |
|                     | 5,695,751    | 12/09/97  | Friedman et al.    |       |          |                               |
|                     | 5,760,230    | 06/02/98  | Schohe-Loop et al. |       |          |                               |
|                     | 5,869,509    | 02/09/99  | Romine et al.      |       |          |                               |
| tz                  | 5,922,735    | 07/13/99  | Sit et al.         |       |          |                               |

**FOREIGN PATENT DOCUMENTS**

|  | DOCUMENT NO. | DATE | COUNTRY | CLASS | SUBCLASS | TRANSLATION |    |
|--|--------------|------|---------|-------|----------|-------------|----|
|  |              |      |         |       |          | YES         | NO |
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| <b>FORM 1449*</b><br><b>INFORMATION DISCLOSURE STATEMENT</b><br><br><b>IN AN APPLICATION</b><br><br>(Use several sheets if necessary) | Docket Number:<br>CEDAR 043453                     | Application Number:<br>09/491,500 |
|   | Applicant: Keith L. Black and Nagendra S. Ningaraj |                                   |
|   | Filing Date: Jan. 26, 2000                         | Group Art Unit: 1646              |

| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) |     |  |
|--|-----|--|
| BS   | 1.  | Adeagbo, A.S., <i>1-Ethyl-2-benzimidazolinone stimulates endothelial K(Ca) channels and nitric oxide formation in rat mesenteric vessels</i> , <u>Eur. J. Pharmacol</u> , 379(2-3):151-9 (August 27, 1999). ABSTRACT ONLY.   |
|  | 2.  | Akar, F., et al., <i>Protective effect of cromakalim and diazoxide, and proulcerogenic effect of glibenclamide on indomethacin-induced gastric injury</i> , <u>Eur. J. Pharmacol</u> , 374(3):461-70 (June 25, 1999). ABSTRACT ONLY.                               |
|  | 3.  | Andrade, S.P., et al., <i>Pharmacological reactivity of neoplastic and non-neoplastic associated neovasculature to vasoconstrictors</i> , <u>Int. J. Exp. Pathol</u> , 79(6):425-32 (December 1998). ABSTRACT ONLY.  |
|  | 4.  | Brian, J.E., Jr., et al., <i>Recent insights into the regulation of cerebral circulation</i> , <u>Clin. Exp. Pharmacol Physiol</u> , 23(6-7):449-57 (June-July 1996). ABSTRACT ONLY.   |
|  | 5.  | Brismar, T., et al., <i>Mechanism of high K<sup>+</sup> and Tl<sup>+</sup> uptake in cultured human glioma cells</i> , <u>Cell Mol. Neurobiol</u> , 15(3):351-60 (June 1995). ABSTRACT ONLY.   |
|  | 6.  | Brismar, T., et al., <i>Thallium-201 uptake relates to membrane potential and potassium permeability in human glioma cells</i> , <u>Brain Res.</u> , 500(1-2):30-6 (October 23, 1989). ABSTRACT ONLY.  |
|  | 7.  | Burg, M.A., et al., <i>NG2 proteoglycan-binding peptides target tumor neovasculature</i> , <u>Cancer Res.</u> , 59(12):2869-74 (June 15, 1999). ABSTRACT ONLY.   |
|  | 8.  | Burrows, F. J., et al., <i>Eradication of large solid tumors in mice with an immunotoxin directed against tumor vasculature</i> , <u>Proc. Natl. Acad. Science U.S.A.</u> , 90(19):8996-9000 (October 1, 1993). ABSTRACT ONLY.                                     |
|  | 9.  | Butt, A.M., <i>Effect of inflammatory agents on electrical resistance across the blood-brain barrier in pial microvessels of anaesthetized rats</i> , <u>Brain Res.</u> , 696(1-2):145-50 (October 23, 1995). ABSTRACT ONLY.                                       |
|  | 10. | Butt, A.M., et al., <i>Effect of histamine and antagonists on electrical resistance across the blood-brain barrier in rat brain-surface microvessels</i> , <u>Brain Res.</u> , 569(1):100-5 (January 8, 1992). ABSTRACT ONLY.                                      |
|  | 11. | Cai, S., et al., <i>Single-channel characterization of the pharmacological properties of the K(Ca<sup>2+</sup>) channel of intermediate conductance in bovine aortic endothelial cells</i> , <u>J. Membr. Biol.</u> , 163(2):147-58 (May 15, 1998). ABSTRACT ONLY. |
|  | 12. | Chang, S.S., et al., <i>Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature</i> , <u>Cancer Res.</u> , 59(13):3192-8 (July 1, 1999). ABSTRACT ONLY.                                |
| BS   | 13. | Chaplin, D.J., et al., <i>Anti-vascular approaches to solid tumour therapy: evaluation of combretastatin A4 phosphate</i> , <u>Anticancer Res.</u> , 19(1A):189-95 (Jan.-Feb. 1999). ABSTRACT ONLY.  |

|   |                 |
|---|-----------------|
| EXAMINER  | DATE CONSIDERED |
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| <b>FORM 1449°</b><br><b>INFORMATION DISCLOSURE STATEMENT</b><br><br><b>IN AN APPLICATION</b><br><br>(Use several sheets if necessary) | Docket Number:<br><b>CEDAR 043453</b>                     | Application Number:<br><b>09/491,500</b> |
|   | Applicant: <b>Keith L. Black and Nagendra S. Ningsanj</b> |  |
|   | Filing Date: <b>Jan. 26, 2000</b>                         | Group Art Unit: <b>1648</b>              |
|   |   |  |

|     |  |
|-----|--|
| 14. | Chassande, O., et al., <i>The Na<sup>+</sup>/K<sup>+</sup>/Cl<sup>-</sup> cotransport in C6 glioma cells, Properties and role in volume regulation</i> , <u>Eur. J. Biochem.</u> , 171(3):425-33 (February 1, 1988). ABSTRACT ONLY.                  |
| 15. | Chess-Williams, R., et al., <i>In vitro investigation of the bladder-vascular selectivity of levcromakalim and YM934 in human tissues</i> , <u>BJU Int.</u> , 83(9):1050-4 (June 1999). ABSTRACT ONLY.   |
| 16. | Dark, G.G., et al., <i>Combretastatin A-4, an agent that displays potent and selective toxicity toward tumor vasculature</i> , <u>Cancer Res.</u> , 57(10):1829-34 (May 15, 1997). ABSTRACT ONLY.  |
| 17. | Denekamp, J., et al., <i>Vasculature and microenvironmental gradients: the missing links in novel approaches to cancer therapy?</i> <u>Adv. Enzyme Regul.</u> , 38:281-99 (1998). ABSTRACT ONLY.   |
| 18. | Desai, S.B., et al., <i>Tumor angiogenesis and endothelial cell modulatory factors</i> , <u>J. Immunother.</u> , 22(3):186-211 (May 1999). ABSTRACT ONLY.  |
| 19. | D'hahan, N., et al., <i>A transmembrane domain of the sulfonylurea receptor mediates activation of ATP-sensitive K(+) channels by K(+) channel openers</i> , <u>Mol. Pharmacol.</u> , 56(2):308-15 (August 1999). ABSTRACT ONLY.                     |
| 20. | Duda, T., <i>Mutations in the Rod Outer Segment Membrane Guanylate Cyclase in a Cone-Rod Dystrophy Cause Defects in Calcium Signaling</i> , <u>Biochemistry</u> , 38(42):13912-13919 (October 19, 1999). ABSTRACT ONLY.                              |
| 21. | Faraci, F.M., et al., <i>Responses of cerebral arterioles to N-methyl-D-aspartate and activation of ATP-sensitive potassium channels in old rats</i> , <u>Brain Res.</u> , 654(2):349-51 (August 22, 1994). ABSTRACT ONLY.                           |
| 22. | Faraci, F.M., et al., <i>Potassium channels and the cerebral circulation</i> , <u>Clin. Exp. Pharmacol Physiol.</u> , 23(12):1091-5 (December 1996). ABSTRACT ONLY.  |
| 23. | Friebe, A., et al., <i>Mechanism of YC-1-Induced activation of soluble guanylyl cyclase</i> , <u>Mol. Pharmacol.</u> , 53(1):123-7 (January 1998). ABSTRACT ONLY.  |
| 24. | Goldstein, G. W., et al., <i>In vitro studies of the blood-brain barrier using isolated brain capillaries and cultured endothelial cells</i> , <u>Ann. N.Y. Acad. Science</u> , 481:202-13 (1986). ABSTRACT ONLY.                                    |
| 25. | Harland, S. P., et al., <i>Expression of endothelin(A) receptors in human gliomas and meningiomas, with high affinity for the selective antagonist PD156707</i> , <u>Neurosurgery</u> , 43(4):890-8; discussion 898-9 (October 1998). ABSTRACT ONLY. |
| 26. | Holland, M., et al., <i>Effects of the BKCa channel activator, NS1619, on rat cerebral artery smooth muscle</i> , <u>Br. J. Pharmacol.</u> , 117(1):119-29 (January 1996). ABSTRACT ONLY.  |
| 27. | Jain, R. K., <i>Vascular and interstitial barriers to delivery of therapeutic agents in tumors</i> , <u>Cancer Metastasis Rev.</u> , 9(3):253-66 (November 1990). ABSTRACT ONLY.   |
| 28. | Keep, R. F., et al., <i>Potassium transport at the blood-brain and blood-CSF barriers</i> , <u>Adv. Exp. Med. Biol.</u> , 331:43-54 (1993). ABSTRACT ONLY.   |

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|   | Applicant: <b>Keith L. Black and Nagendra S. Ningara</b> |  |
|   | Filing Date: <b>Jan. 26, 2000</b>                        | Group Art Unit: <b>1646</b>              |

|    |     |   |
|----|-----|---|
| RS | 29. | Konoshita, H., et al., <i>Differential effects of lidocaine and mexiletine on relaxations to ATP-sensitive K<sup>+</sup> channel openers in rat aortas</i> , <u>Anesthesiology</u> , 90(4):1165-70 (April 1999). ABSTRACT ONLY.   |
| 1  | 30. | Kitazono, T., et al., <i>Role of potassium channels in cerebral blood vessels</i> , <u>Stroke</u> , 26(9):1713-23 (September 1995). ABSTRACT ONLY.  |
|    | 31. | Lee, Y.S., et al., <i>In vitro antitumor activity of cromakalim in human brain tumor cells</i> , <u>Pharmacology</u> , 49(2):69-74 (August 1994). ABSTRACT ONLY.  |
|    | 32. | Manor, D., et al., <i>Interactions among calcium compartments in C6 rat glioma cells; involvement of potassium channels</i> , <u>J. Physiol. (Lond.)</u> , 478(Pt.2):251-63 (July 15, 1994). ABSTRACT ONLY.   |
|    | 33. | Miller, T.R., et al., <i>Pharmacological and molecular characterization of ATP-sensitive K<sup>+</sup> channels in the TE671 human medulloblastoma cell line</i> , <u>Eur. J. Pharmacol.</u> , 370(2):179-85 (April 9, 1999). ABSTRACT ONLY.                            |
|    | 34. | Molema, G., et al., <i>Tumor vascular endothelium: barrier or target in tumor directed drug delivery and immunotherapy</i> , <u>Pharm. Res.</u> , 14(1):2-10 (January 1997). ABSTRACT ONLY.   |
|    | 35. | O'Donnell, M.E. et al., <i>Cerebral microvascular endothelial cell Na-K-Cl cotransport: regulation by astrocyte-conditioned medium</i> , <u>Am. J. Physiol.</u> , 268(3 Pt. 1):C747-54 (March 1995). ABSTRACT ONLY.   |
|    | 36. | Ohizumi, I., et al., <i>Antibody-based therapy targeting tumor vascular endothelial cells suppresses solid tumor growth in rats</i> , <u>Biochem Biophys. Res. Commun.</u> , 236(2):493-6 (July 18, 1997). ABSTRACT ONLY.   |
|    | 37. | Ohta, Y., et al., <i>Tumor angiogenesis and recurrence in stage I non-small cell lung cancer</i> , <u>Ann. Thorac. Surg.</u> , 68(3):1034-8 (September 1999). ABSTRACT ONLY.  |
|    | 38. | Panchal, R.G., <i>Novel therapeutic strategies to selectively kill cancer cells</i> , <u>Biochem Pharmacol.</u> , 55(3):247-52 (February 1, 1998). ABSTRACT ONLY.   |
|    | 39. | Patel, H.J., et al., <i>Inhibition of cholinergic neurotransmission in guinea pig trachea by NS1619, a putative activator of large-conductance, calcium-activated potassium channels</i> , <u>J. Pharmacol. Exp. Ther.</u> , 286(2):952-8 (August 1998). ABSTRACT ONLY. |
|    | 40. | Ran, S., et al., <i>Infarction of solid Hodgkin's tumors in mice by antibody-directed targeting of tissue factor to tumor vasculature</i> , <u>Cancer Res.</u> , 58(20):4646-53 (October 15, 1998). ABSTRACT ONLY.  |
|    | 41. | Redrobe, J.P., et al., <i>The effect of the potassium channel activator, cromakalim, on antidepressant drugs in the forced swimming test in mice</i> , <u>Fundam. Clin. Pharmacol.</u> , 10(6):524-8 (1996). ABSTRACT ONLY.   |
| RS | 42. | Rettig, W.J., et al., <i>Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer</i> , <u>Proc. Natl. Acad. Sci. U.S.A.</u> , 89(22):10832-6 (November 15, 1992). ABSTRACT ONLY.  |

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| EXAMINER  | DATE CONSIDERED |
| EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant. |                 |

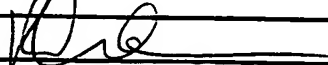
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| <b>FORM 1449<sup>o</sup></b><br><b>INFORMATION DISCLOSURE STATEMENT</b><br><br><b>IN AN APPLICATION</b><br><br>(Use several sheets if necessary) | Docket Number:<br><b>CEDAR 043453</b>                     | Application Number:<br><b>09/491,500</b> |
|  | Applicant: <b>Keith L. Black and Nagendra S. Ningaraj</b> |  |
|  | Filing Date: <b>Jan. 26, 2000</b>                         | Group Art Unit: <b>1646</b>              |

|     |  |
|-----|--|
| 43. | Revest, P.A., et al., <i>The transendothelial DC potential of rat blood-brain barrier vessels in situ</i> , <u>Adv. Exp. Med. Biol.</u> , 331:71-4 (1993). ABSTRACT ONLY.  |
| 44. | Revest, P.A., et al., <i>Transendothelial electrical potential across pial vessels in anaesthetised rats: a study of ion permeability and transport at the blood-brain barrier</i> , <u>Brain Res.</u> , 652(1):76-82 (July 25, 1994). ABSTRACT ONLY.                          |
| 45. | Sandstrom, P.E., et al., <i>Identification of potassium flux pathways and their role in the cytotoxicity of estramustine in human malignant glioma, prostatic carcinoma and pulmonary carcinoma cell lines</i> , <u>Eur. J. Cancer</u> , 30A(12):1822-6 (1994). ABSTRACT ONLY. |
| 46. | Schilling, L., et al., <i>Opening of the blood-brain barrier during cortical superfusion with histamine</i> , <u>Brain Res.</u> , 653(1-2):289-96 (August 8, 1994). ABSTRACT ONLY.   |
| 47. | Serfass, L., et al., <i>Effect of heme oxygenase inhibitors on soluble guanylyl cyclase activity</i> , <u>Arch. Biochem. Biophys.</u> , 359(1):8-16 (1998). ABSTRACT ONLY.   |
| 48. | Sobey, C.G., et al., <i>Mechanisms of bradykinin-induced cerebral vasodilatation in rats. Evidence that reactive oxygen species activate K<sup>+</sup> channels</i> , <u>Stroke</u> , 28(11):2290-4; discussion 2295 (November 1997). ABSTRACT ONLY.                           |
| 49. | Smoak, I.W., <i>Cromakalim: embryonic effects and reduction of tolbutamide-induced dysmorphogenesis in vitro</i> , <u>Teratology</u> , 60(5):260-264 (November 1999). ABSTRACT ONLY.   |
| 50. | Sugai, K. et al., <i>Levcromakalim decreases cytoplasmic Ca<sup>2+</sup> and vascular tone in basilar artery of SAH model dogs</i> , <u>J. Cardiovasc. Pharmacol.</u> , 33(6):868-75 (June 1999). ABSTRACT ONLY.   |
| 51. | Teramoto, N. et al., <i>Comparative studies on the relaxing action of several adenosine 5'-triphosphate-sensitive K<sup>+</sup> channel openers in pig urethra</i> , <u>J. Smooth Muscle Res.</u> , 35(1):11-22 (February 1999). ABSTRACT ONLY.                                |
| 52. | Thorpe, P. E. et al., <i>Antibody-directed targeting of the vasculature of solid tumors</i> , <u>Breast Cancer Res. Treat.</u> , 36(2):237-51 (1995). ABSTRACT ONLY.   |
| 53. | Toyoda, K. et al., <i>Role of ATP-sensitive potassium channels in brain stem circulation during hypotension</i> , <u>Am. J. Physiol.</u> , 273(Pt. 2):H1342-6 (September 1997). ABSTRACT ONLY.   |
| 54. | Van Hinsbergh, V. W. et al., <i>Angiogenesis and anti-angiogenesis: perspectives for the treatment of solid tumors</i> , <u>Ann. Oncol.</u> , 10 Supl 4:60-3 (1999). ABSTRACT ONLY.  |
| 55. | Walter, J. J. et al., <i>Angiostatin binds to smooth muscle cells in the coronary artery and inhibits smooth muscle cell proliferation and migration In vitro</i> , <u>Arterioscler. Throm. Vasc. Biol.</u> , 19(9):2041-8 (September 1999). ABSTRACT ONLY.                    |
| 56. | Wickenden, A.D. et al., <i>Comparison of the effects of the K(+)-channel openers cromakalim and minoxidil sulphate on vascular smooth muscle</i> , <u>Br. J. Pharmacol.</u> , 103(1):1148-52 (May 1991). ABSTRACT ONLY.  |

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| EXAMINER   | DATE CONSIDERED <b>3/20/07</b> |
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Page 1 of 1

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## FOREIGN PATENT DOCUMENTS

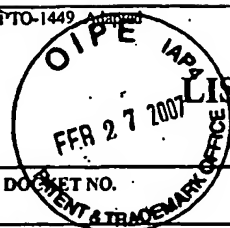
| EXAMINER<br>INITIAL | DOCUMENT NUMBER | DATE                | COUNTRY | CLASS | SUB<br>CLASS | TRANSLATION<br>Yes | TRANSLATION<br>No |
|---------------------|-----------------|---------------------|---------|-------|--------------|--------------------|-------------------|
| KS                  | WO 91/16355     | 31.10.91            | PCT     | 1     | 7            |                    |                   |
|                     | WO 97/31654     | 04.09.97            | PCT     |       |              |                    |                   |
|                     | WO 00/23102     | 27.04.00            | PCT     |       |              |                    |                   |
|                     | 0 351 767 A2    | 24.01.90 Bul. 90/04 | EP      |       |              |                    |                   |
|                     | 0 555 681 A1    | 18.08.93 Bul. 93/33 | EP      |       |              |                    |                   |
| LS                  | 0 575 749 A2    | 29.12.93 Bul. 93/52 | EP      |       |              |                    |                   |
|                     |                 |                     |         |       |              |                    |                   |

**OTHER ART (Including Author, title, Date, Pertinent Pages, Etc.)**

|     |  |
|-----|--|
| 57. | XP-002195899 - Oak, Z. et al., <i>Effects of Cyclic GMP on Microvascular Permeability of the Cerebral Cortex</i> , <u>Microvascular Research</u> , Vol. 58, pp. 35-40 (1999).            |
| 58. | XP-002195900 - Role of nitric oxide in histamine-induced increases in permeability of the blood-brain barrier, <u>Mayhan, William G., Brain Research</u> , Vol. 743, pp. 70-76 (1996).   |
| 59. | XP-002195901 - Bartus, R. T. et al., <i>Controlled Modulation of BBB Permeability Using the Bradykinin Agonist, RMP-07</i> , <u>Experimental Neurology</u> , Vol. 142, pp. 14-28 (1996). |
| 60. | International Search Report re PCT/US01/02743, P mailed 26/04/2002   |
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| EXAMINER  | DATE CONSIDERED; |
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FORM 10-1449

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| ATTY. DOCKET NO. | SERIAL NO. | FILING DATE      |
|                  | 09/491,500 | January 26, 2000 |

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| Keith L. Black and Nagendra S. Ningaraj | 1632  |

**U.S. PATENT DOCUMENTS**

| EXAMINER INITIAL | DOCUMENT NUMBER | DATE     | NAME       | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
|------------------|-----------------|----------|------------|-------|----------|----------------------------|
| RS               | AA 5,518,499    | 05/21/06 | Agar       |       |          |                            |
| RS               | AB 5,767,160    | 06/16/98 | Kaesemeyer |       |          |                            |

**OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)**

|    |    |  |
|----|----|--|
| RS | AC | Armstead, W.M., Contribution of kca channel activation to hypoxic cerebrovasodilation does not involve NO, <u>Brain Res</u> , 799:44-48 (1998). ABSTRACT ONLY.   |
|    | AD | Barna, M., et al., Activation of type III nitric oxide synthase in astrocytes following a neurotropic viral infection, <u>Virology</u> , 223: 331-343 (1996).  |
|    | AE | Becker, E.M., et al., The vasodilator-stimulated phosphoprotein (VASP): target of YC-1 and nitric oxide effects in human and rat platelets, <u>J Cardiovasc Pharmacol</u> , 35(3):390-7 (2000). ABSTRACT ONLY.                                       |
|    | AF | Boje, K.M., Inhibition of nitric oxide synthase attenuates blood-brain barrier disruption during experimental meningitis, <u>Brain Research</u> , 720:75-83 (1996).  |
|    | AG | Brandt, L., et al., Effects of topical application of calcium antagonist (nifedipine) on feline cortical pial microvasculature under normal conditions and in focal ischemia, <u>Journal of Cerebral Blood Flow and Metabolism</u> , 3:44-50 (1983). |
|    | AH | Brioni, J.D., et al., Activators of soluble guanylate cyclase for treatment of male erectile dysfunction, <u>International Journal of Impotence Research</u> , 14:8-14 (2002).   |
|    | AI | Bychkov, R., et al. Calcium-activated potassium channels and nitrate-induced vasodilation in human coronary arteries, <u>J Pharmacol Exp Therap</u> , 285:293-8 (1998). ABSTRACT ONLY.   |
|    | AJ | Chandran, S., et al., Nitric oxide: concepts, current perspectives and future therapeutic implications, <u>Indian Journal of Pharmacology</u> , 30:351-366 (1998).   |
|    | AK | Chi, O.Z., et al. Effect of inhibition of nitric oxide synthase on blood-brain barrier transport in focal cerebral ischemia, <u>Pharmacology</u> , 48:367-373 (1994).  |
|    | AL | Cloughesy, T.F., et al., Pharmacological blood-brain barrier modification for selective drug delivery, <u>Journal of Neuro-Oncology</u> , 26:125-132 (1995).   |
|    | AM | Feelisch, M., The use of nitric oxide donors in pharmacological studies, <u>Naunyn-Schmiedeberg's Arch Pharmacol</u> , 358:113-122 (1998).   |
|    | AN | Fukao, M., et al., Cyclic GMP-dependent protein kinase activates cloned BKCa channels expressed in mammalian cells by direct phosphorylation at serine 1072, <u>J Biol Chem</u> , 274(16):10927-35 (1999).   |
|    | AO | Fukumura, D., et al., Role of nitric oxide in angiogenesis and microcirculation in tumors, <u>Cancer and Metastasis Reviews</u> , 17:77-89 (1998).   |
|    | AP | He, P., et al., cGMP modulates basal and activated microvessel permeability independently of [Ca <sup>2+</sup> ] <sub>i</sub> , <u>Am J Physiol</u> , 274:H1865-74 (1998). ABSTRACT ONLY.  |
| RS | AQ | Herrera, G.M., et al., Maintained vasodilatory response to cromakalim after inhibition of nitric oxide synthesis, <u>J Cardiovasc Pharmacol</u> , 31:921-9 (1998). ABSTRACT ONLY   |

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| EXAMINER           | DATE CONSIDERED |
| <i>[Signature]</i> | 3/26/07         |

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FORM PTO-1449, Adapted

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**OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)**

|    |    |  |
|----|----|--|
| DS | AR | Holschermann, H., et al., <i>Dual role of cGMP in modulation of macromolecule permeability of aortic endothelial cells</i> , <u>Am J Physiol</u> , 272:H91-8 (1997). ABSTRACT ONLY.  |
|    | AS | Hongli, X., et al., <i>Opening blood-brain-barrier by intracarotid infusion of papaverine in treatment of malignant cerebral glioma</i> , <u>Chinese Medical Journal</u> , 111(8):751-753 (1998).  |
|    | AT | Hurst, R.D., et al., <i>Nitric oxide-induced perturbations in a cell culture model of the blood-brain barrier</i> , <u>Journal of Cellular Physiology</u> , 167:89-94 (1996).  |
|    | AU | Inamura, T., et al., <i>Intracarotid histamine infusion increases blood tumour permeability in RG2 glioma</i> , <u>Neurological Research</u> , 16:125-128 (1994).  |
|    | AV | Inamura, T., et al., <i>Intracarotid infusion of RMP-7, a bradykinin analog: a method for selective drug delivery to brain tumors</i> , <u>J Neurosurg</u> , 81:752-758 (1994).  |
|    | AW | Janigro, D., et al., <i>Regulation of blood-brain barrier endothelial cells by nitric oxide</i> , <u>Circulation Research</u> , 75:528-528 (1994).   |
|    | AX | Kimura, M., et al., <i>Responses of human basilar and other isolated arteries to novel nitric oxide donors</i> , <u>J Cardiovasc Pharmacol</u> , 32: 695-701 (1998). ABSTRACT ONLY.  |
|    | AY | Koesling, D., <i>Modulators of soluble guanylyl cyclase</i> , <u>Naunyn-Schmiedeberg's Arch Pharmacol</u> , 358:123-126 (1998).  |
|    | AZ | Liu, Y., et al., <i>Repeated, short-term ischemia augments bradykinin-mediated opening of the blood-tumor barrier in rats with RG2 glioma</i> , <u>Neurological Research</u> , 23:631-639 (2001).  |
|    | BA | Lohse, M.J., et al., <i>Pharmacology of NO:cGMP signal transduction</i> , <u>Naunyn-Schmiedeberg's Arch Pharmacol</u> , 358:111-112 (1998).  |
|    | BB | Matukado, T., et al., <i>Selective Increase in Blood Tumor Permeability by Calcium Antagonists in Transplanted Brain Tumors</i> , <u>Acta Neurochir</u> , 60: 403-405 (1994).  |
|    | BC | Mayer, B., et al., <i>Nitric oxide synthases: catalytic function and progress toward selective inhibition</i> , <u>Naunyn-Schmiedeberg's Arch Pharmacol</u> , 358:127-133 (1998).  |
|    | BD | Mayhan, W.G., <i>Role of nitric oxide in histamine-induced increases in permeability of the blood-brain barrier</i> , <u>Brain Research</u> , 743:70-76 (1996).  |
|    | BE | Mayhan, W.G., et al., <i>Glutamate-induced disruption of the blood-brain barrier in rats</i> , <u>Stroke</u> , 27:965-970 (1996).  |
|    | BF | Nakano, S., et al., <i>Increased brain microvessel permeability after intracarotid bradykinin infusion is mediated by nitric oxide</i> , <u>Cancer Research</u> , 56:4027-4031 (1996).   |
| RS | BG | Ningaraj, N.S., et al., <i>Role of ATP-sensitive K<sup>+</sup> channels in blood-brain tumor barrier permeability</i> , <u>Congress of Neurological Surgeons Annual Meeting</u> , 50 <sup>th</sup> Anniversary Celebration, September 23-28, 2000, Henry B. Gonzalez Convention Center, San Antonio, Texas, ABSTRACT No. 4309, p. 215. |

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| BH   |  | Ningaraj, N.S., et al., Ca <sup>2+</sup> -dependent K <sup>+</sup> channels are a key regulatory of blood-brain tumor barrier permeability, <u>Congress of Neurological Surgeons Annual Meeting</u> , 50 <sup>th</sup> Anniversary Celebration, September 23-28, 2000, Henry B. Gonzalez Convention Center, San Antonio, Texas, ABSTRACT No.428, p. 219. |                                 |
| BI   |  | Ningaraj, N.S., et al., Nitric oxide donors increase blood-brain tumor barrier permeability via Kca channels, <u>Society for Neuroscience</u> , 30 <sup>th</sup> Annual Meeting, New Orleans, LA, November 4-9, 2000, 26 Part 1, p. 338, ABSTRACT No. 126.8.   |                                 |
| BJ   |  | Ningaraj, N.S., et al., Regulation of blood-brain tumor barrier permeability by calcium-activated potassium channels, <u>The Journal of Pharmacology</u> , June 2002, 301: 838-851   |                                 |
| BK   |  | Pardrige, W., et al., Blood-brain barrier and new approaches to drug delivery, <u>West J Med</u> , 156:281-286 (1992).   |                                 |
| BL   |  | Robertson, B.E., et al., cGMP-dependent protein kinase activates Ca-activated K channels in cerebral artery smooth muscle cells, <u>Am J Physiol</u> , 265:C299-C303 (1993).   |                                 |
| BM   |  | Sobey, C.G., et al., Inhibitory effect of 4-aminopyridine on responses of the basilar artery to nitric oxide, <u>Br J Pharmacol</u> , 126:1437-43 (1999). ABSTRACT ONLY.   |                                 |
| BN   |  | Salom, J.B., et al., Relaxant effects of sodium nitroprusside and NONOates in rabbit basilar artery, <u>Pharmacology</u> , 57:79-97 (1998). ABSTRACT ONLY.   |                                 |
| BO   |  | Salom, J.B., et al., Comparative relaxant effects of the NO donors sodium nitroprusside, DEA/NO and SPER/NO in rabbit carotid arteries, <u>Gen Pharmacol</u> , 32:75-59 (1999). ABSTRACT ONLY.   |                                 |
| BP   |  | Salom, J.B., et al., Relaxant effects of sodium nitroprusside and NONates in goat middle cerebral artery: delayed impairment of global ischemia-reperfusion, <u>Nitric Oxide</u> , 3:85-93 (1999). ABSTRACT ONLY.  |                                 |
| BQ   |  | Shukla, A., et al., Nitric oxide-dependent blood-brain barrier permeability alteration in the rat brain, <u>Experientia</u> , 52:136-140 (1996).   |                                 |
| BR   |  | Smolenski, A., et al., Functional analysis of cGMP-dependent protein kinases I and II as mediators of NO/cGMP effects, <u>Naunyn-Schmiedeberg's Arch Pharmacol</u> , 358:134-138.  |                                 |
| BS   |  | Sugita, M., et al., Cyclic GMP-specific phosphodiesterase inhibition and intracarotid bradykinin infusion enhances permeability in brain tumors, <u>Cancer Research</u> , 58:914-920 (1998).   |                                 |
| BT   |  | Takayasu, M., et al., Effects of calcium antagonists on intracerebral penetrating arterioles in rats, <u>J Neurosurg</u> , 69:104-109 (1988).  |                                 |
| BU   |  | Uchida, M., et al., Overexpression of bradykinin type 2 receptors on glioma cells enhances bradykinin-mediated blood-brain tumor barrier permeability increase, <u>Neurological Research</u> , 24:739-745  |                                 |
| EXAMINER   |  |  | DATE CONSIDERED                 |
| EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. |  |  |                                 |

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| <b>OTHER REFERENCES</b> (Including Author, Title, Date, Pertinent Pages, Etc.)   |    |   |                                 |
| PS   | BV | Uchida, M., et al., <i>Cyclic GMP-dependent blood-brain tumor barrier permeability is not mediated by cyclic GMP-dependent protein kinase</i> , <u>Congress of Neurological Surgeons Annual Meeting</u> , 50 <sup>th</sup> Anniversary Celebration, September 23-28, 2000, Henry B. Gonzalez Convention center, San Antonio, Texas, ABSTRACT No. 440, p. 220. |                                 |
|  | BW | Vodovotz, Y., et al., <i>Regulation of transforming growth factor beta 1 by nitric oxide</i> , <u>Cancer Res.</u> 59:2142-9 (1999). ABSTRACT ONLY.  |                                 |
|  | BX | Yukabu, M.A., <i>Hematoma-induced enhanced cerebral vasoconstriction to leukotriene C4 and endothelin-1 piglets: role of prostanoids</i> , <u>Pediatr Res.</u> 38:119-23 (1995). ABSTRACT ONLY.   |                                 |
|  | BY | Tocris Web Page, <a href="http://www.tocris.com/cat/nodonorstxt.html">http://www.tocris.com/cat/nodonorstxt.html</a> No Donors/Precursors, pp.1-2, Downloaded 5/31/00.  |                                 |
| TS   | BZ | Sigma-Aldrich Web page, <a href="http://vsearch.sial.com/search_97cgi/s97-cgi">http://vsearch.sial.com/search_97cgi/s97-cgi</a> , p.1, downloaded 5/31/00.  |                                 |
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